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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/780,752	02/09/2001	Kirk P. Conrad	CONN-001	6620

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EXAMINER	
LIU, SAMUEL W	

ART UNIT	PAPER NUMBER
1653	7

DATE MAILED: 11/27/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/780,752	CONRAD ET AL.	
	Examiner	Art Unit	
	Samuel W Liu	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 October 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-27* is/are pending in the application.

4a) Of the above claim(s) *20-27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *3* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of Claims

Claims 1-27 are pending.

The information disclosure statement filed May 21 2001has been entered and the references listed in the statement have been considered. The drawing filed 19 September 200 have been approved by US PTO drafting.

Election/Restrictions

Applicant's election of Group I, Claims 1-19 with traverse filed 28 October 2002 (Paper No. 6) is acknowledged. The traverse is on the ground that all the groups should be examined together without burden to the examiner. Applicants' assertion has been fully considered. But it is unpersuasive because each group was set forth properly and shown to have different classification, art area and recognized divergent subject matter. It would require therefore a undue burden on the examiner to have searched all claims drawn to the different inventions.

Claims 20-27 are withdrawn from consideration as being directed to a non-elected invention. Claims 1-19 are pending and examined in this Office action.

Specification/Claim/ Objections

The disclosure is objected to because of the following informalities:

In page 4, line 15, the terms "MAP", GRF", "ERPF", "ERVR" should be spelled out in full at the first instance of use. See also page 4, line 21, "RT-PCR" and line 22, VEGF"; page 14, line 12, "PCR"; and line 28 "FGF"; and page 25, line12, "cGMP".

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter that the applicant regards as his invention.

Claims 1-8, 10-15 and 18-19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The dependent claims are also rejected.

Claim 4 is indefinite in recitations of "...about 0.1 to 500 μg/kg..."; it is ambiguous as to what is encompassed in these limitations. The recitation appears to set "±" parameter on lower number or/and both lower number and higher number ends of the "% range". Such the recitation includes numerous possibilities of the relaxin dosage to be administered to the patient. See also claims 4, 7, 8, 10, 11, 14, 15, 18 and 19.

Claim 5 recites "time sufficient to ..."; the recitation is unclear because the term sufficient is undefined in the specification as to what time point the therapeutic effect can be obtained. See also claims 7-8, 11, 15 and 19.

Claim 11 recites "...wherein ...recombinant human relaxin ...". There is insufficient antecedent basis for this limitation in claim 9 from which claim 11 depends because claim 9 does not recites "*recombinant* human relaxin". See also claims 15 and 19.

Claim 12 recites "increase a parameter associated with"; the recitation is not apparent because "parameter" *per se* in general refers to a constant whose value characterizes a member

or system; does relaxin change characteristics of renal function permanently? Suggest "a factor". The dependent claims are also included in the rejection.

Claim 17 is vague because the recitation "an ischemic wound" is not apparent as to whether or not the recitation refers to a special clinical case or a pathological state in general of ischemic wound. See also the recitation "an ischemic cardiac condition" in the claim.

Claim Rejections - 35 USC §102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

9-14-99 3-23-6

Claims 1-2, 4, 6, 8-11 and 14-19 are rejected under 35 U.S.C. 102 (a) as being anticipated by Bigazzi, M. (US Pat. No. 5952296).

Bigazzi teaches a method of treating hypertension comprising administering pharmaceutically active relaxin to a patient (see abstract, column 8, lines 46-47 and lines 55-60, and patent claim 1), as applied to claims 1 of the instant application.

Renal hypertension, namely, renovascular hypertension, is characterized by renal high blood pressure caused by narrowing of the arties the carry blood to the kidneys. Bigazzi teaches that (i) relaxin actively acts on vascular dilation (*i.e.*, vasodilation) of organs' arteries (see column 3, lines 51-52); (ii) one of targets of relaxin actions is kidney (see column 4, lines 1-2); and (iii) relaxin is a pharmaceutical composition for treating disorder states, *e.g.*, hypertension (see column 8, lines 55-58); the hypertension includes renovascular hypertension, a pathological pregnancy complication. Because Bigazzi also teaches that during pregnancy relaxin promotes

the renal vascular system undergoing a new arrangement (see column 8, lines 2-4), the Bigazzi's patent anticipates a renal hypertension, the limitation set forth in the application claim 2.

Bigazzi teaches that relaxin is active on the vascular system, *e.g.*, increasing vasodilation of arterioles (see column 8, lines 40-42), as applied to claim 9 of instant application.

Bigazzi teaches a method of increasing renal function (see column 8, lines 1-12, 39-46 and 50-54) by enhancing a "parameter" associated with renal function, *i.e.*, glomercular filtration (see column 8, lines 5-7) comprising administering to a patient formulated relaxin (see claim 1 and 29), as applied to claims 12 and 13 of the current application.

Also, Bigazzi discloses a method of treating an ischemic condition comprising administering to a patient an effective amount of relaxin (see patent claims 1-2 and 29-34) and circulatory vascular ischemic disease (see patent claim 29), as applied to claims 16 and 17 of the instant application.

In addition, Bigazzi teaches that administration dose of relaxin to rat is 10 μg which is equivalent to about 400 μg/kg (based on that rat weight is 250 grams) (see column7, lines 18-19) and teaches an injectable formulation (see column 6, lines 12-14). Thus, the Bigazzi teaching anticipates claims 4, 6, 8, 10-11, 14-15 and 18-19 of the instant application.

Claims 9-15 are rejected under 35 U.S.C. 102 (a) as being anticipated by Danielson, L. A. *et al.* (*J. Clin. Invest.* (1999) 103, 525-533).

Danielson *et al.* teach that relaxin increases vasodilation (see abstract lines 3-7, and discussion section at page 529), which comprises administering relaxin to the patient (see page 526, the right column the forth paragraph), as applied to claim 9 of the instant application.

Also, Danielson *et al.* teach a process of treating a mammal with either purified relaxin or *recombinant* human relaxin (rhRLX); the treatment results in effective renal plasma flow and glomerular filtration rate increased by 20%–40% (see abstract and Figure 2 (b) –(d)). The reference data suggest an ability of the relaxin of enhancing renal function parameter, *i.e.*, glomerular filtration rate significantly. Thus, the Danielson *et al.* reference anticipates the application claims 12 and 13.

In addition, Danielson *et al.* teach administering relaxing to rat with 4 μg dose per hour which is equivalent to about 200 μg/kg dose (based on that rat weight is 250 grams) (see "Experimental protocols". Thus, the Bigazzi teaching also anticipates claims 10-11 and 14-15 of the instant application.

Claim Rejections - 35 USC §102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

The claims 16-19 are rejected under 35 U.S.C. 102(e) as being anticipated by Unemori, E. (US Pat. No. 6211147).

Unemori discloses a method of a method of treating an ischemic condition, *e.g.*, ischemic wound, comprising administering pharmaceutically active relaxin to a patient (see abstract, "summary of the invention" at column 2, and column 5, lines 3-9), as applied to claims 16 and 17 of the instant application.

Also, Unemori teaches that (i) the relaxin used is a *recombinant* relaxin (see column 2, lines 50-51), (ii) the administering dosage is from about 0.1 to 500 μg/kg of body weight, and (iii) therapeutic formulation is an injectable formulation (see column 2, lines 4-5, where states that "formulations of human relaxin are described in U.S. application No. 08/050,745"; now, it is US Pat. No. 5451572). Thus, the Unemori reference anticipates the application claim 18 and 19.

Claim Rejections - 35 USC §103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-2 and 4-19 are rejected under 35 U.S.C. 103(a) as being obvious over Bigazzi, M. (US Pat. No. 5952296) taken with Unemori, E. (US Pat. No. 6211147).

Bigazzi teaches a method of treating hypertension comprising administering pharmaceutically active relaxin to a patient (see abstract and column 8, lines 46-47, column 8, lines 55-60, and claim 1), as applied to claim 1 of the instant application.

Bigazzi also teaches a method of increasing renal function (see column 8, lines 1-12 and 39-46) by enhancing a "parameter" associated with renal function, *i.e.*, glomercular filtration (see column 8, lines 5-7) comprising administering to a patient formulated relaxin (see patent claim 1 and 29), as applied to claims 12 and 13 of the current application. In addition, the Bigazzi's patent teaches the subject matter of the application claim 2, *i.e.*, treating renal hypertension (see the corresponding rejection under 35 USC 102 (a) set forth in the foregoing).

Bigazzi teaches that relaxin is active on the vascular system, *e.g.*, increasing vasodilation of arterioles (see column 8, lines 40-42), as applied to claim 9 of instant application.

Further, Bigazzi discloses a method of treating an ischemic condition comprising administering to a patient an effective amount of relaxin (see patent claims 1-2 and 29-34) and circulatory vascular ischemic disease (see patent claim 29), as applied to claims 16 and 17 of the instant application.

Since Bigazzi also teaches administration dose of relaxin to rat is 10 μg, which is equivalent to about 400 μg/kg dose (based on that rat weight is 250 grams) (see column7, lines 18-19, and column 6, lines 12-14), the Bigazzi's patent anticipates claims 4, 6, 8, 10-11, 14-15 and 18-19 of the instant application.

However, the Bigazzi patent does not explicitly disclose specific relaxin administration route to a patient.

Unemori teaches that (i) the dosage for the administration is from about 0.1 to 500 μg/kg of body weight (see column 4, lines 23-24) for treating disease state, *e.g.*, diabetes that is hypertension-related (see column 1, lines 12-15), as applied to the application claims 4 and 8; (ii) the relaxin is a *recombinant* relaxin (see column 2, lines 50-51), as applied to claim 8 of the current application; (iii) therapeutic formulation is an injectable formulation (see column 2, lines 1-5, where recites that "formulations of human relaxin are described in U.S. Pat. Application No.. 08/050,745"; now it is US Pat No. 5451572), as applied to the application claim 6; (iv) continuing administration is performed over a period sufficient to obtain a therapeutic effect on the patient (see claim 1), as applied to the application claim 5; and (v) relaxin is administered in such a way that a serum concentration of relaxin is achieved at 0.5 to 50 ng/ml (see column 4), as applied to the application claim 7.

One of ordinary skill in the art would have combined the teachings of Bigazzi and Unemori *et al.* to develop a method of treating hypertension comprising administering the therapeutically formulated relaxin or recombinant relaxin.

Because administering to subject and administering process set forth in both the references is the same, *i.e.*, the subject is a mammal, the route of the administration is indistinct, and target disease states are related, and because the Unemori reference especially teaches more details regarding administering the relaxin formulation (see column 5, lines 3-16), the skilled artesian would have been motivated to incorporate the Unemori teaching with respect to the dosage, formulation form and route of administration into the method of relaxin-directed

treatment of hypertension and ischemic condition as well as increasing renal function as taught by Bigazzi.

Thus, the claimed invention was prima facie obvious to make and use at the time it was made.

Claims 9-19 are rejected under 35 U.S.C. 103(a) as being obvious Danielson, L. A. *et al.*, (*J. Clin. Invest.* (1999) 103, 525-533) taken with Unemori, E. (US Pat. No. 6211147).

Danielson *et al.* teach that increase of vasodilation by relaxin comprising administering *recombinant* relaxin to the patient (see abstract lines 3-7, page 529 discussion, and page 526, the forth paragraph of the right column), as applied to claim 9 of the instant application. Also, Danielson *et al.* teach a process of increasing renal function comprising treating a mammal with either purified relaxin or recombinant human relaxin, which results in effective renal plasma flow and glomercular filtration rate increased by 20%–40% (see the abstract and Figure 2 (b) – (d)). These data demonstrate that the relaxin is capable of increasing renal function via acting on the parameter, *i.e.*, glomercular filtration rate that measures renal function, as applied to claims 12 and 13.

However, Danielson *et al.* do not teach treating an ischemic disorder and administrating route thereof.

Unemori discloses a method of a method of treating an ischemic condition, *e.g.*, ischemic wound, comprising administering pharmaceutically active relaxin to a patient (see abstract, "summary of the invention" at column 2, and column 5, lines 3-9), as applied to claims 16 and 17 of the instant application.

Unemori teaches that (i) the relaxin used is a *recombinant* relaxin (see column 2, lines 50-51), (ii) the administering dosage is from about 0.1 to 500 μg/kg of body weight, and (iii) therapeutic formulation is an injectable formulation (see column 2, lines 4-5, where states that "formulations of human relaxin are described in U.S. application No. 08/050,745"; now, it is US Pat. No. 5451572). Thus, the Unemori reference anticipates the application claim 18 and 19.

Unemori (US Pat. No. 6211147) also explicitly teaches that (i) the dosage for the administration is from about 0.1 to 500 μg/kg of body weight (see column 4, lines 23-24) for treating vascular disorder states (see column 1, lines 10-15 and column 3, lines 5-8), as applied to the application claims 10-11 and 14-15; (ii) therapeutic formulation is an injectable formulation, which has been disclosed in the reference incorporated (see the foregoing statement), as applied to the application claim 11; (iii) administration is performed over a period sufficient to obtain a therapeutic effect on the patient (see claim 1), as applied to the application claim 15; and (v) the relaxin is a *recombinant* relaxin (see column 2, lines 50-51), as applied to claims 11 and 15 of the current application.

One of ordinary skill in the art would have combined the teachings of Danielson *et al.* and Unemori *et al.* to develop a method of treating vasodilation and a method of increasing renal function comprising administering to a subject the therapeutically active relaxin or the recombinant relaxin.

Because the administration subject and process set forth in both the references is the same, *i.e.*, a mammal, the route of the administration is indistinct and target disease states are related, and because the Unemori reference especially teaches more details regarding administering the relaxin formulation (see column 5, lines 3-16), the skilled artesian would have

been motivated to incorporate the Unemori teaching with respect to the dosage, formulation form and route of administration into the Danielson's method in order to increase vasodilation and renal function as well as to treat ischemic condition, *e.g.*, ischemic wound.

Thus, the claimed subject matter of claims 9-15 was prima facie obvious to make and use at the time it was made.

Claim Rejection –Obviousness Type Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

Claims 16-19 are rejected under the judicially created doctrine of the obviousness-type double patenting of Claim 29 in United States Patent No. 5952296. Although the conflicting claims are not identical, they are not patentably distinct from each other.

Claims 16 and 17of the current application and claim 29 of US Pat. No. 5952296 disclose the same subject matter. Claim 29 discloses a method of treating an ischemic condition comprising administering an effective amount of relaxin (see column 11, line 67) to a patient (see column 11, line 59). Although the scope of Claim 29 is different from that of Claim 1, the subject matter disclosed in claim 29 is identical to that of Claim 16 the instant application. Thus, claim 29 is an obvious variation of claim 16.

Since the disclosure of US Pat. No. 5952296 sets forth that the invention is destined to reduce the volume of circulating blood in congestive heart failure (see column 4, lines 5-6), and since ischemic cardiac condition, is the most common cause of congestive heart failure, the recitation of "treating a condition, *e.g.*, circulatory vascular ischemic disease..." of patent claim 29 (see column 11, lines 43-50) is an obvious variation of the application claim 17.

Further, US Pat No. 5952296 sets forth that the administration dose of relaxin is 10 μg, which is equivalent to about 160 μg/kg (based on that rat weight is 250 grams), and that relaxin is administered by injection route (see column 7, lines 18-19, and column 6, lines 12-14). The reference patent disclosure, therefore, is an obvious variation of claims 18 and 19 of the instant application.

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b). Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Samuel Wei Liu whose telephone number is (703) 306-3483. The examiner can normally be reached from 9:00 a.m. to 5:00 p.m. on weekdays. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Christopher

Low, can be reached on 703 308-2923. The fax phone number for the organization where this application or proceeding is assigned is 703 308-4242 or 703 872-9306 (official) or 703 872-9307 (after final). Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703 305-4700.

Karen Cochrane Carlson PhD

KAREN COCHRANE CARLSON, PH.D
PRIMARY EXAMINER

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November 14, 2002